
Table 4: *Relationship of characteristics of newborns of preeclamptic mothers to their in-hospital mortality.*

Risk factors	G1	G2	P	Odds ratio	CI (95%)
Characteristics of the neborns at the birth					
ale gender			5		21-2
Gestational age eeks of gestation		5		92	19-1
Gestational age 1d - eeks of gestation d			1		1-21
Gestational age eeks of gestation		2	19	29	-15
irth eight 15 (g) 1			2	5	225-95
irth eight 15-2 (g)	1		5		-
irth eight 2- (g)	5		5	25	-1
IUGR			51	12	51-5
ysharmonic IUGR	2	5	5	19	-
armonious IUGR		1	1	1	12-9
pgar at 1 minute 22			1	9	12-1

Stay in NICU ≥ 3 days	27	8	0,022	4,8	[1,18-19,46]
Apgar at 5 minutes ≤ 8	27	9	0,002	9,5	[1,92-47,08]
Apparent state of death	5	1	0,532	1,58	[0,16-14,92]
Neonatal morbidities	16	5	0,061	3,54	[0,96-13,70]
Respiratory distress syndrom	2	4	0,001	23,43	[3,63-151,19]
Infectious alveolitis	31	1	0,394	2,7	[0,25-28,49]
Congenital heart disease	1	2	0,035	18,22	[1,50-221,36]
Necrotizing enterocolitis	2	8	<0,001	109,33	[15,85-753,9]
Hemodynamic disorder	1	9	<0,001	373,5	[30,75-4536,79]
Intraventricular hemorrhage	2	2	0,065	9,11	[1,14-72,73]
Materno fetal infection	17	8	0,001	10,51	[2,52-43,90]
Nosocomial infection	5	6	<0,001	18,96	[4,26-84,27]
Jaundice	24	4	0,726	1,43	[0,38-6,33]
hypocalcemia	6	5	0,003	10,83	[2,54-46,11]
hypoglycemia	6	1	0,590	1,30	[0,14-11,93]
Anemia	6	4	0,015	7,43	[1,68-32,72]
Thrombocytopenia	18	6	0,027	4,4	[1,20-16,08]
Leukopenia	12	3	0,372	2,25	[0,52-9,69]
Polycythemia	7	2	0,279	2,44	[0,44-13,69]
CPAP Ventilation	9	6	0,002	10	[2,53-39,49]
Invasive ventilation	1	7	<0,001	145,25	[14,23-1482,64]
Hospital stay in NICU ≥ 3 days	30	8	0,024	4,8	[1,18-19,46]

Multivariate study

In order to identify the independent factors related to hospital mortality in MEP NN, we conducted a multivariate analysis using stepwise descending logistic regression. The variables chosen were those with p values less than 0.05 in the univariate study. We selected 10 of the 19 significant variables obtainedin the univariate analysis. Table V summarizes the variables used in the multivariate study. In this multivariate analysis, three risk factors independently related to in-hospital mortality in MEP NN were identified.

Table 5: *The variables used in the multivariate study.*

Risk factors	**G1**	**G2**	**P**	**Odds ratio**	**CI (95%)**
Onset of PE ≤ 32 WG	16	6	0,017	5,1	[1,38-18,82]
HELLP syndrome	13	6	0,007	6,55	[1,74-24,68]
Gestational age ≤ 30 WG	8	5	0,006	7,92	[1,96-31,86]
Birth weight<1500 (g)	14	7	0,002	8,75	[2,25-33,95]
Apgar at 5 minutes ≤ 8	27	9	0,002	9,5	[1,92-47,08]
Neonatal hypocalcemia	6	5	0,003	10,83	[2,54-46,11]
Anemia	6	4	0,015	7,43	[1,68-32,72]
Thrombocytopenia	18	6	0,027	4,4	[1,20-16,08]
CPAP Ventilation	9	6	0,002	10	[2,53-39,49]
Stay in NICU ≥ 3 days	30	8	0,024	4,8	[1,18-19,46]

The risk factors for in-hospital mortality of BEP NNs and the risk factors independently related to in-hospital mortality of BEP NNs based on the multivariate study (Table 6).

Table 6: *Risk factors for in-hospital mortality in newborns of pre-eclamptic mothers.*

Univariate study	**P**	**Odds ratio**	**IC (95%)**
Onset of PE ≤ 32 WG	0,017	5,1	[1,38-18,82]
HELLP syndrome	0,007	6,55	[1,74-24,68]
Gestational age ≤ 30 WG	0,006	7,92	[1,96-31,86]
Birth weight<1500 (g)	0,002	8,75	[2,25-33,95]
Apgar at 1 minute ≤ 7	0,031	4,93	[1,32-18,48]
Apgar at 5 minutes ≤ 8	0,002	9,5	[1,92-47,08]
MMH	0,001	23,43	[3,63-151,19]
Congenital heart disease	0,035	18,22	[1,50-221,36]
Necrotizing enterocolitis	<0,001	109,33	[15,85-753,9]
Hemodynamic disorder	<0,001	373,5	[30,75- 4536,79]
Materno fetal infection	0,001	10,51	[2,52-43,90]
Nosocomial infection	<0,001	18,96	[4,26-84,27]
Neonatal hypocalcemia	0,003	10,83	[2,54-46,11]
Anemia	0,015	7,43	[1,68-32,72]
Thrombocytopenia	0,027	4,4	[1,20-16,08]
CPAP Ventilation	0,002	10	[2,53-39,49]
Invasive ventilation	<0,001	145,25	[14,23-1482,64]
Vasoactive drugs	<0,001	373,5	[30,75- 4536,79]
Length of stay in NICU ≥ 3 days	0,024	4,8	[1,18-19,46]
Multivaried study	P	Odds ratio	IC (95%)
EP complicated by HELLP syndrome	0,036	7,42	[1,14 - 48,19]
Neonatal hypocalcemia	0,007	16,80	[2,16 – 130,56]
Use of CPAP ventilation in NN	0,011	10,59	[1,7 – 66,05]

The risk factors independently associated with in-hospital mortality for NN of pre-eclamptic mothers are summarized (Table 7).

Table 7: *The risk factors independently associated with in-hospital mortality for NN of pre-eclamptic mothers.*

Risk factor	**p**	**OR**	**IC (95%)**
EP complicated by HELLP syndrome	0,036	7,42	[1,14-48,19]
Neonatal hypocalcemia	0,007	16,80	[2,16-130,56]
Use of CPAP ventilation in NN	0,011	10,59	[1,7-66,05]

Discussion

Preeclampsia is a frequent pathology responsible for a significant maternal and neonatal morbidity and mortality [5]. To date, few studies have assessed the impact of this condition and the quality of its management on neonatal prognosis in our country. The objective of our study was to describe the epidemiological, clinical and evolutionary profile of newborns of preeclamptic mothers and to identify their risk factors for

hospital mortality [6]. Our study was retrospective, monocentric over a period of 6 months from July 1 to December 31, 2020 and included 95 live births of preeclamptic mothers initially managed in the "A" and "C" obstetrics gynecology departments of the CMNT [7]. We excluded fetal death, NN with a PN birth weight lower than 700 grams and/or less than 27 weeks of gestation. The prevalence of EP was 2.35% with a prevalence of severe and moderate forms that were respectively 1.73% and 0.62%. Although the overall prevalence of EP in our study is similar to that of developed countries, we note that it differs in the preponderance of preponderance of severe EP compared to moderate EP [8]. Indeed, a longitudinal study in Canada over 24 years on a large database that included 1.9 million births and 68010 cases of EP, the incidences of moderate and severe EP were respectively 2.57% and 0.89%. The mean maternal age was 31.44 ± 5.71 years and 59.1% of parturients were older than 30 years [9]. Our results are consistent with those who found respectively for this age group 71.3% and 69.8% of the two populations studied, with an average age of 28.5 years and 31.5 years. This age range represents in our socio-cultural context the age of marriage and maximum procreation. Indeed, according to the

Multiple Indicator Cluster Survey (MICS) of Tunisia was conducted in 2018 by the National Institute of Statistics in collaboration with the Ministry of Development Investment and International Cooperation (MDICI) under the global program of MICS 6 surveys [10]. Women aged between 30 and 34 years have the highest fertility rate and to a lesser extent those aged between 25 and 29 years. Parental consanguinity was noted in 29.5% of cases. This rate is close to that reported in the literature [11]. In a study published in 2007, conducted in Monastir, to determine the prevalence of consanguinity and its effects on fertility and mortality in Tunisia, 1741 live births from 1989 to 1991, consanguinity in the Tunisian population was 24.8%. Studies on the effect of consanguinity on EP are contradictory [12]. In a review of the literature, which aimed to study the consequences of inbreeding on reproduction,the authors noted that in some studies that inbreeding does not seem to increase the risk of but on the contrary decrease it. Other studies have shown that there was no association between inbreeding and EP, nor on the development of maternal-fetal complications [13]. In a study in Holland, which aimed to analyze the relationship of family aggregation and consanguinity with EP and IUGR for 106 women in a genetically isolated area in Holland, the percentage of women born of a consanguineous marriage was higher in women with a history of EP compared to the control group [14]. The authors observed that the co-segregation of EP and IUGR supports a common genetic etiology and that the high rate of parental consanguineous marriages suggests the possibility of an underlying recessive genetic mutation. 56.8% of mothers were primiparous. Parturients reported a family history of hypertension and PE in 47.3% and 4.3% of cases, respectively [15]. A personal history of maternal pathology was noted in 27.4% of cases. Maternal pathologies were dominated by chronic hypertension, diabetes, asthma and hypothyroidism and were noted in 6.3%, 6.3%, 5.3% and 4.2% of cases respectively. A history of PE and fetal death was reported in 70% and 40% of the multiparous women respectively. Primiparity was noted in 56.8% of parturients. During the gestational period, gestational hypertension was noted in 30.5% of cases, 55.2% of which occurred before 34 weeks' gestation. Gestational diabetes was observed in 16.8% of parturients. Our results are consistent with those of the literature [16]. The literature states that multiparous patients with a history of EP, MFIU or other complications of EP represent a population at high risk of developing a second episode of EP, especially in its severe forms that can be identified early in pregnancy [17]. Thus, a history of EP has been shown to be a significant risk factor in many studies with a recurrence rate that varies between 14 and 50% according to the publications [18]. A retrospective German study, including 647, 392 pregnancies from the German Perinatal Quality Registry, aimed to examine the relationship between gestational diabetes and EP after controlling for common risk factors. The authors found that the risk of EP was increased in women with gestational diabetes with an adjusted Odds Ratio (OR): 1.29, 95% CI: 1.19-1.41), even after controlling for age, nationality, occupational status, smoking, parity, multiple pregnancy and weight gain during pregnancy [19]. A retrospective German study, including 647,392 pregnancies from the German Perinatal Quality Registry, aimed to examine the relationship between gestational diabetes and EP after controlling for common risk factors. The authors found that the risk of EP was increased in women with gestational diabetes with an adjusted Odds ratio (aOR): 1.29, 95% CI: 1.19-1.41), even after controlling for age, nationality, occupational status, smoking, parity, multiple pregnancy and weight gain during pregnancy [20]. In a systematic review of the literature, which included 149 controlled studies, it was found that a family history of EP triples the risk of EP, that nulliparity triples the risk of EP, and that mothers with a history of this disease have a sevenfold increased risk of developing EP.

The mean gestational age of discovery of EP was 34.38 ± 3.27 weeks of gestation. EP was late and early respectively in 69.5% and 30.5% of cases [21]. For perinatal outcome, the studies noted a high incidence of fetal growth restriction resulting in low birth weight in the EP NNs; almost one third of them had weight below the 10^{th} percentile for their gestational age. There was also a higher rate of perinatal mortality [22]. Our results are consistent with the literature. Indeed, a significant association was found between hospital mortality and NN of mothers whose EP occurred before 32 SA (p=0.017). Severe EP was most frequent in 73.7% of cases and moderate in 26.3% of cases. Our results differ from the literature in the distribution of EP severity [23]. The high prevalence of severe EP in our study can be explained by the fact that the Tunis maternity center recruits mainly high-risk pregnancies subject to both maternal and neonatal complications [24]. The high prevalence of severe EP in our study can be explained by the fact that the Tunis maternity center recruits essentially high-risk pregnancies and subject to both maternal and neonatal complications [25]. The evolution of EP was marked by the occurrence of complications in 30.5% of cases. HELLP syndrome was the most frequent

complication in 20% of cases. In a systematic review of the literature, HELLP syndrome complicates 10 to 20% of severe EP and develops in 50% of cases before 34 weeks' gestation. Perinatal morbidity and mortality is significantly higher in NN of mothers with HELLP syndrome. The perinatal mortality rate of HELLP syndrome varies between 7.4% and 34% and depends mainly on the gestational age at delivery. Our results are consistent with those of the literature with a statistically significant association between hospital mortality and NN of MEPs with HELLP syndrome (p=0.007) and a neonatal mortality of 32% for the latter. In our study, a female predominance was noted with a gender ratio (M/F) of 0.73. Our results are in agreement with those of the literature.

In our study, the mean gestational age was 35.02 ± 3.15 SA with extremes of 27 and 39 SA. The number of preterm NN was 64.2%. This rate was higher than that found in the literature. A study conducted in the United States from 1990 to 2004 on 57 million newborns showed that hypertensive disorders of pregnancy (gestational hypertension and EP) are associated with a greater risk of stillbirth and neonatal mortality and that the risk of prematurity is multiplied by 4 in mothers with EP compared to those with normotension [26]. In our study, prematurity with gestational age ≤ 30 weeks of gestation was significantly associated with in-hospital mortality (p=0.006). In our study, 23.2% of NN had a weight less than or equal to 1500 g. They were eutrophic in 53.7% of cases. IUGR was noted in 41% of the cases, it was considered disharmonious and severe respectively in 82% and 38.5% of the IUGR cases. The relationship between EP and IUGR is well studied in the literature. Indeed, EP is present as a result of abnormal placentation that can lead to delayed placental development, lack of oxygenation and nutrition of the fetus responsible for IUGR. EP affects the placental blood supply, resulting in IUGR and may lead to preterm delivery [27]. It is estimated that there are 30 million newborns with IUGR in low-and middle-income countries, with one in seven births associated with EP. The mean Apgar scores at 1 and 5 minutes were 7.62 ± 1.97 and 8.42 ± 1.95, respectively. The Apgar scores at 1 and 5 minutes were considered low in 15.8% and 13.7% of cases, respectively. In a univariate study, we found a significant association between a low Apgar score and in-hospital mortality in NN, with a score less than or equal to 7 at 1 minute (p=0.031) and less than or equal to 8 at 5 minutes (p=0.002).

These results are in line with the data demonstrated by the study with a lower Apgar score more frequent in NN of mothers with severe EP and associated with maternal complications. Among the intra-hospital comorbidities, we noted in our study a statistically significant association between the occurrence of respiratory distress syndrome (p=0.001). Among the in-hospital comorbidities, there was a statistically significant association between the occurrence of respiratory distress syndrome (p=0.001), congenital heart disease (p=0.036), SIMF (p=0.001), nosocomial infection (p<0.001), neonatal anemia and thrombocytopenia (p=0.015 and p=0.027), neonatal hypocalcemia in univariate and multivariate analysis (p=0.003 and p=0.007), and in-hospital mortality in NN of EP mothers [28]. The literature has largely focused on the study of the involvement of these risk factors identified in our study, in this sense, it contains divergent opinions on the effect of EP of occurrence or not of respiratory distress. In a Chinese study, on a large cohort of 185,687 live births, aiming to determine the association between maternal hypertension and EP with DRNN, that EP is a risk factor for the occurrence of DRNN and infectious alveolitis not only for preterm newborns but also for those born at term. In a Canadian study, which included 1,942,072 newborns, which aimed to determine the risk of congenital heart disease in newborns of EPM, the risk of EP is more frequent in newborns of EPM with a prevalence of 16.7/1000 births.

The authors found that there was a significant association between EP and the occurrence of non-severe congenital heart disease and that early EP was associated with severe congenital heart disease. The authors also noted that ductus arteriosus persistence is more common in NN of EP compared to those of normotensive mothers. In a systematic review of the literature, aimed at studying the long-term infectious morbidity of children of MEP, although severe EP is associated with a higher risk of infectious morbidity in these children. This association is thought to be due to prematurity and mode of delivery by caesarean section rather than the EP itself. In a 3-year retrospective study in the USA to determine the association between EP and necrotizing enterocolitis, 4.6% necrotizing enterocolitis in newborns of EPM and concluded that EP is a risk factor for necrotizing enterocolitis in newborns of EPM, especially those with IUGR. Neonatal neutropenia is a common hematological disorder in newborns withMEP, especially in preterm infants. It is often of short duration but can be prolonged and severe. This type of neutropenia during the first week after birth potentiates the subsequent risk of infection, especially for preterm infants. The literature contains conflicting opinions on the effect of magnesium sulfate on neonatal calcium levels. Some studies report a significant correlation between the total dose of magnesium sulfate and neonatal serum calcium [29]. The management of newborns of EP mothers allowed us to identify a number of risk factors for mortality related to the use of invasive mechanical ventilation (p<0.001) and CPAP (p=0.002) and the use of vasoactive drugs (p<0.001). Our results are in line with the literature. In a retrospective study in India, during 20 months, aiming to study the neonatal complications of MEP NN, 13% of MEP NN had received mechanical ventilation, 10% CPAP ventilation and 25% Hood oxygen therapy [30]. None of the newborns of normotensive mothers received mechanical ventilation or CPAP. Similarly, it has been reported in the literature that the use of vasoactive drugs is associated with greater neonatal mortality after adjustment for gender, gestational age and 5-minute Apgar score.

A statistically significant association was found between the duration of hospitalization in NICU greater than 3 days and in-hospital mortality of BEP (p=0.024). In this sense, a statistically significant relationship between the duration of hospitalization in NICU and the NN of BEP with a longer duration in the NN of BEP with a positive correlation between

neonatal complications especially neonatal mortality and the duration of hospitalization in NICU. In our study, in-hospital mortality was 11.6% of total cases [31]. The mean survival age of deceased NN was 10.09 ± 11.98 days with extremes of 2 and 44 days. Prematurity was noted in 81.8% of the deceased cases, of which 66.6% were very premature. Low birth weight was noted in 63.6% of the deceased NN. IUGR was noted in 54.5% of the deceased cases. necrotizing enterocolitis was the most frequent direct cause of death of the newborns in 45.5% of cases. The relationship between prematurity and low birth weight is well studied in the literature. In fact, in a study carried out in Holland, the aim was to evaluate the neonatal morbidity and mortality in newborns of mothers with early onset of PE and to compare it with that of newborns of the same gestational age [32]. Newborns with EP had higher perinatal (13% *vs*. 7%) and infant (16% *vs.* 9%) mortality compared to the control group. The authors noted that preterm infants with MEP were twice as likely to have low birth weight compared to preterm infants of similar gestational age born to non-pre-eclamptic mothers. They also concluded that low birth weight is a risk factor for perinatal mortality in EPM NN. Neonatal mortality in our study is higher than that reported in BEP NNs from developed countries but less than that from developing countries [33]. This is consistent with the data in the literature. Indeed, infant mortality is 3 times higher in NEPs in low- and middle-income countries than in developed countries. EP can cause up to 12% of low birth weight in newborns and 20% of prematurity. In the World Health Organization (WHO) WHO Multicountry Survey (WHOMCS), which included 308,392 pregnancies from 29 different countries and aimed to determine the risk of perinatal mortality in mothers with severe pregnancy complications, the authors concluded that for live births, NN of EP had a perinatal mortality rate of 7.2% which is higher than that of NN of non-preeclamptic mothers.

Conclusion

Pre-eclampsia is a frequent pathology responsible for a significant maternal and neonatal morbidity and mortality. To date, few studies have assessed the impact of this condition and the quality of its management on neonatal prognosis in our country. The objective of our study was to describe the epidemiological, clinical and evolutionary profile of newborns of preeclamptic mothers and to identify their risk factors for hospital mortality.

In univariate analysis, we found a significant association between in-hospital mortality of MEP NN and the following variables: EP complicated with HELLP syndrome (p=0.007); term of discovery of EP ≤ 32SA (p=0.017); gestational age of birth of NNs ≤ 30 SA (p=0.006); birth weight <1500g (p=0.002); Apgar score at 1 minute (p=0.031); Apgar score at 5 minutes (p=0.002); respiratory distress syndrome (p=0.001); congenital heart disease (p=0.035), hemodynamic disorders (p<0.001), ECUN (p<0.001); neonatal anemia (p=0.015); neonatal thrombocytopenia (p=0.027); neonatal hypocalcemia (p=0.003); healthcare-associated infection (p<0.001); suspected maternal-fetal infection (p=0.001); use of vasoactive drugs (p<0.001); use of antibiotics (p=0.001); use of CPAP ventilation in NN (p=0.002); use of invasive ventilation in NN (p<0.001) and hospital stay in NN in NICU ≥ 3 days (p=0.024). On multivariate analysis, EP complicated with HELLP syndrome (p=0.036), neonatal hypocalcaemia (p=0.007) and use of CPAP ventilation in NN (p=0.011) were identified as risk factors independently related to in-hospital mortality in NN of BEP.

Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' Contribution

Sdiri Y and Cherifi E have given substantial contributions to the conception and the design of the manuscript, Ayari F and Kacem S to acquisition of the data, Belhaj Ammar W and Chourou H to analysis and interpretation of the data.

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*Correspondence to

Dr. Ayari F

Department of Emergency

University Tunis El Manar

Tunis

Tunisia

E-mail: ayarifeirouz@yahoo.fr